

**This Page Is Inserted by IFW Operations  
and is not a part of the Official Record**

## **BEST AVAILABLE IMAGES**

**Defective images within this document are accurate representations of the original documents submitted by the applicant.**

**Defects in the images may include (but are not limited to):**

- **BLACK BORDERS**
- **TEXT CUT OFF AT TOP, BOTTOM OR SIDES**
- **FADED TEXT**
- **ILLEGIBLE TEXT**
- **SKEWED/SLANTED IMAGES**
- **COLORED PHOTOS**
- **BLACK OR VERY BLACK AND WHITE DARK PHOTOS**
- **GRAY SCALE DOCUMENTS**

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problems Mailbox.**



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61K 9/22, 9/70</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 92/04890</b> <b>(43) International Publication Date:</b> <b>2 April 1992 (02.04.92)</b>
<b>(21) International Application Number:</b> PCT/US91/06397 <b>(22) International Filing Date:</b> 9 September 1991 (09.09.91) <b>(30) Priority data:</b> 585,445 20 September 1990 (20.09.90) US <b>(71) Applicant:</b> THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). <b>(72) Inventor:</b> DAMANI, Nalinkant, Chunilal ; 9823 Meadow Bluff Lane, Cincinnati, OH 45241 (US). <b>(74) Agent:</b> REED, T., David; The Procter & Gamble Com- pany, Ivorydale Technical Ctr., 5299 Spring Grove Ave., Cincinnati, OH 45217-1087 (US).		<b>(81) Designated States:</b> AT (European patent), AU, BE (Euro- pean patent), BR, CA, CH (European patent), DE (Eu- ropean patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European pa- tent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> SUSTAINED RELEASE COMPOSITIONS FOR TREATING PERIODONTAL DISEASE  <b>(57) Abstract</b>  This invention relates to devices/compositions and methods for treating diseases of the oral cavity in humans and lower animals using non-biodegradable devices/compositions which are biocompatible but not bioerodible for releasing drugs in or around a periodontal pocket or gingival sulcus.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU <sup>+</sup>	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TC	Togo
DE*	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

<sup>+</sup> Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

## SUSTAINED RELEASE COMPOSITIONS FOR TREATING PERIODONTAL DISEASE

TECHNICAL FIELD

5           This invention relates to compositions/devices for treating diseases of the oral cavity which compositions/devices are placed in or around the periodontal pocket or gingival sulcus. The invention also relates to methods of using the compositions/devices in humans and lower animals suffering from such diseases.

10           Periodontal disease, for example, is a major cause of tooth loss in adults. Tooth loss from periodontal disease is a significant problem beginning at age 35, but even by age 15 it is estimated that about 4 out of 5 persons already have gingivitis and 4 out of 10 have periodontitis.

15           While good oral hygiene, as achieved by brushing the teeth with a cleansing dentifrice, may help reduce the incidence of periodontal disease, it does not necessarily prevent or eliminate its occurrence. This is because microorganisms contribute to both the initiation and progress of periodontal disease. Thus, in  
20           order to prevent or treat periodontal disease, these microorganisms must be suppressed by some means other than simple mechanical scrubbing. Towards this end, there has been a great deal of research aimed at developing therapeutic dentifrices, mouthwashes, and methods of treating periodontal disease which are  
25           effective in suppressing these microorganisms.

          Recent developments in the art are directed toward delivering the therapeutic agent directly to the periodontal pocket, in some cases in a controlled release formulation. Goodson et al. have described the use of a drug-filled polymer hollow fiber. (J.M.  
30           Goodson et al., "Periodontal Therapy by Local Delivery of Tetracycline", J. Clin. Periodontol. 6, 83 (1979), J. Lindhe et al., "Local Tetracycline Delivery Using Hollow Fiber Devices in Periodontal Therapy", J. Clin. Periodontol. 6, 141 (1979) and R.L. Dunn

## 2.

et al., "Monolithic Fibers for Controlled Delivery of Tetracycline", in Proc. Ninth Int. Symposium on Controlled Release of Bioactive Materials, Ft. Lauderdale, FL, July (1982). This device is tied around a tooth and gently pressed below the margin of the gingiva so that it resides in the periodontal pocket, and is capable of delivering an effective dose of 2.5 micrograms of tetracycline per day per periodontal pocket for a prolonged period of a week or more. Similar results have been obtained by Coventry and Newman (J. Coventry and H. N. Newman, "Experimental Use of a Slow Release Device Employing Chlorhexidine Gluconate in Areas of Acute Periodontal Inflammation", J. Clin. Periodontol. 9, 129 (1982) and Addy et al. (M. Addy et al., "The Development and in vitro Evaluation of Acrylic Strips and Dialysis Tubing for Local Drug Delivery", J. Periodontol. 53, 693 (1982) using acrylic strips 1mm or more long, impregnated with chlorhexidine, tetracycline or metronidazole, which were inserted into the periodontal pocket with tweezers. Such a strip, formed from ethylcellulose impregnated with metronidazole, is disclosed by Loesche in U.S. Patent No. 4,568,538 (February 1986). Another strip, employing a water soluble polymer of a particular elasticity and viscosity, is disclosed by Suzuki et al. in U.S. Patent No. 4,569,837.

In addition to the above approaches, the prior art also discloses using putty-like compositions containing an antimicrobial for insertion into the periodontal pocket. A material disclosed as suitable is a copolymer of lactide and glycolide. See U.S. Patent 4,650,665, March 17, 1987 to Kronenthal et al., incorporated herein by reference.

The present inventor has found that a small chip, cone or strip loaded to a fairly high level with drug active can provide excellent release of the active into or around the periodontal pocket.

It is, therefore, an object of the present invention to provide devices/compositions suitable for use in or around the periodontal pocket.

## 3.

It is a further object of the present invention to provide devices/compositions which are constructed of particular polymers.

It is still a further object of the present invention to provide a method of treating periodontol disease.

5 All percentages and ratios used in here are by weight unless otherwise indicated.

All measurements are made at 25°C unless otherwise indicated.

#### SUMMARY OF INVENTION

10 The present invention relates to devices/compositions and methods for treating diseases of the oral cavity by inserting the devices/compositions into the periodontol pocket or around said pocket of humans and/or lower animals suffering from such diseases. The devices/compositions comprise biocompatible, non-bioerodible polymers and an agent providing relief of oral  
15 cavity diseases. The devices/compositions are flexible and solid and have approximate size and shape for simple placement at a disease site.

#### DETAILED DESCRIPTION OF THE INVENTION

20 The essential as well as optional components of the devices/compositions of this invention are described below.

##### Biocompatible/Non-Bioerodible Polymers

The polymers which are useful in forming the compositions/articles of the present invention include any polymer which is not bioerodible, is biocompatible and is capable of being formed into  
25 a solid. Included are polymers such as polyurethanes, ethylene vinyl acetate copolymers, collagen, poly isobutylene, cellulosic polymers, ethylene vinyl alcohol copolymers, polystyrene, polyvinyl chloride, polycarbonate, and polyethylene among many others.

The preferred polymers are ethylene vinyl acetate, poly isobutylene and polyurethane with ethylene vinyl acetate being the  
30 preferred material.

##### Drug Active

The drugs useful for use in the present devices/compositions are varied and many and include any agent which provides treatment  
35 or prevention management of diseases of the oral cavity. Some therapeutic agents which are amenable to delivery by this means

## 4.

and are potentially of value for periodontol therapy, include (but are not limited to) antibacterial and antifungal agents such as iodine, triclosan sulfonamides, mercurials, bisbiguanides or phenolics; antibiotics such as the tetracyclines, neomycin, kanamycin, metronidazole, or clindamycin; antiinflammatory agents such as aspirin, naproxen, ibuprofen, flurbiprofen, indomethacin, eugenol, or hydrocortisone; anticalculus agents such as any of the soluble pyrophosphate salts some of which are described in U.S. Patent 4,515,772, May 7, 1985 to Parran incorporated herein by reference; immune-suppressive or stimulatory agents such as methotrexate or levamasole; dentinal desensitizing agents such as strontium chloride or sodium fluoride; odor masking agents such as peppermint oil or chlorophyll; immune reagents such as immunoglobulins or antigens; local anesthetic agents such as lidocaine or benzocaine; nutritional agents such as amino acids, essential fats, and vitamin C; antioxidants such as alpha-tocopherol and butylated hydroxy toluene; lipopolysaccharide complexing agents such as polymyxin; or peroxides such as urea peroxide. It is recognized that in certain forms of therapy, combinations of these agents in the same delivery system may be useful in order to obtain an optimal effect. Thus, for example, an antibacterial and an antiinflammatory agent may be combined in a single delivery system to provide combined effectiveness.

The drug active is used at a level of from about 0.5% to about 95%, preferably from about 15% to about 85%, most preferably from about 20% to about 80% of the devices/compositions. The devices/compositions, for example, are designed to release drug to provide steady state average concentrations of active of from about 10 $\mu$ g to about 5000 $\mu$ g, preferably from about 25 $\mu$ g to about 2500 $\mu$ g, most preferably from about 50 $\mu$ g to about 2000 $\mu$ g per milliliter of the gingival crevicular fluid of a treated periodontol pocket, per one device unit. The steady state release rates can be altered by varying component ratios of the compositions, as well as by amount of device at a treatment site. The steady state conditions are preferably used since initial bursts

## 5.

are accounted for as well as delays in release. For example, in the case of a ten (10) day therapy, average steady state is generally reached in about one to two days.

#### Optional Components

5 In addition to the drug active, the devices/compositions of the present invention may include a variety of optional components. Such components include, but are not limited to, surfactants, viscosity controlling agents, complexing agents, anti-oxidants, other polymers such as carboxymethyl cellulose, gums  
10 such as guar gum, waxes/oils such as castor wax, castor oil, glycerol, dibutyl phthalate and di(2-ethylhexyl) phthalate as well as many others. If used, these optional components comprise from about 0.1% to about 20%, preferably from about 0.5% to about 5% of the total composition/device.

15 The devices/compositions of this invention are in shapes such as strips, chips or cones. The sizes of these shapes will generally fall into the following ranges:

#### Strips

20	Average Thickness:	0.75 ( $\pm$ 0.5 mm)
	Average Width:	1.0 ( $\pm$ 0.5 mm)
	Average Length:	Cut as needed to fit a pocket, generally ranging from about 3 mm to about 12 mm

#### Chips

25	Average thickness:	0.75 ( $\pm$ 0.5 mm)
	Average width of pointed end:	0.3 ( $\pm$ 0.25 mm)
	Average width of wider end:	1.5 ( $\pm$ 0.5 mm)
	Average Length:	15 ( $\pm$ 5 mm)

The length is cut at either end to fit a periodontal cavity  
30 by a dental professional at the time of use.

#### Cones

	Average pointed end diameter:	0.25 ( $\pm$ 0.2 mm)
	Average thicker end diameter:	1.5 ( $\pm$ 0.5 mm)
	Average length of cone:	15 ( $\pm$ 5 mm)

35 The length is cut at either end to fit a periodontal cavity by a dental professional at the time of use.



METHOD OF MANUFACTURE

Method of manufacturing the devices/compositions of this invention are disclosed following the Examples for the purpose of illustration.

5       The following Examples further describe and demonstrate the preferred embodiments within the scope of the present invention. The Examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention as many variations thereof are possible without departing from its  
10       spirit and scope.

EXAMPLE 1

The following is an exemplary composition/device of the present invention.

	<u>Parts per 100</u>
15       Tetracycline hydrochloride	70
Ethylene-vinyl Acetate	30

EXAMPLE 2

The following is another exemplary composition/device of the present invention.

	<u>Parts per 100</u>
20       Metronidazole	57
Bis(2-ethylhexyl) Phthalate	3
Ethylene-vinyl Acetate	40
25       Bis(2-ethylhexyl) phthalate is dioctyl phthalate, and is used as a plasticizer to increase diffusion of a drug from the polymer.	

EXAMPLE 3

The following is another exemplary composition/device of the present invention.

	<u>Parts per 100</u>
30       Minocycline hydrochloride	60
Sodium chloride	5
Ethylene-vinyl Acetate	35
35       Sodium chloride, as a soluble salt, provides an increase in internal osmotic pressure to increase drug release from the device.	

## 7.

EXAMPLE 4

The following is yet another exemplary composition of the present invention.

		<u>Parts per 100</u>
5	Clindamycin hydrochloride	30
	Liquid paraffin	7
	Poly isobutylene (low molecular weight)	26
	Poly isobutylene (high molecular weight)	37
10	Liquid paraffin or mineral oil is a solvent plasticizer for poly isobutylene.	

EXAMPLE 5

The following is another exemplary composition of the present invention.

		<u>Parts per 100</u>
15	Chlorhexidine diacetate	35
	Tetra sodium pyrophosphate	10
	Polyurethane	55
	Pyrophosphate is included to provide effects on dental calculus.	

EXAMPLE 6

20 The following is another exemplary composition of the present invention.

		<u>Parts per 100</u>
	Ciprofloxacin	30
	Poly isobutylene	20
25	Polypropenoic acid	10
	Polyurethane	40
30	<del>Polypropenoic acid</del> is included in this example to absorb subgingival fluid, to keep the application site dry for the poly isobutylene component to develop adhesiveness at the application site.	

The above described devices/compositions may be prepared by charging the polymer into a jacketed and heated mixer equipped with high shear Sigma type rotor blades. The mixer is heated to a temperature to melt or soften the polymer. The drug is added to the mixer and the mixing process is continued until a homogeneous blend is obtained. Additives other than a drug and polymer can be added to obtain a homogeneous blend.

## 8.

5       The composition blend is removed from the mixer, and is  
compressed between platens of a hydraulic press such as a Carver  
press, using spacers to obtain the desired thickness. Although not  
necessary, it is desirable to have the platens of the hydraulic  
press jacketed, which allows heating and cooling of the material  
during the compression process. Upon compression, the material is  
obtained in form of a uniform thickness film. Devices of this  
development are cut into suitable size and shape using this film.  
10       Cone shaped devices, for example, are prepared from thin films  
having thickness of about 0.01 mm and rolling to form a cone  
shape.

Other alternative mixing and forming methods may be used to  
obtain devices/compositions of this invention. The appropriate  
sizes and shapes are set forth on page 5 of this application.

15       WHAT IS CLAIMED:

20

25

30

35

-9-

## CLAIMS:

1. A solid composition suitable for insertion into the periodontol pocket or the gingival sulcus of a person or lower animal suffering from diseases of the oral cavity comprising a non-biodegradable, biocompatible polymer and a drug active selected from the group consisting of antiinflammatory agents, antimicrobials, antibiotics, peroxides, anesthetic agents and vitamins in a concentration from about 0.5% to about 95% wherein said composition is in the form of a chip, cone or strip and wherein said composition provides steady state average concentrations of active of from about 10mg to about 5000mg, preferably from about 25mg to about 2500mg per milliliter of the gingival crevicular fluid of a treated periodontol pocket or gingival sulcus.
2. A composition according to Claim 1 wherein the polymer is selected from the group consisting of polyurethanes, ethylene vinyl acetate copolymers, collagen, poly isobutylene, cellulosic polymers, ethylene vinyl alcohol copolymers, polyethylene polycarbonate, and polyvinyl chloride.
3. A composition according to Claim 2 wherein the concentration of the drug active is from about 15% to about 85% and the active is selected from the tetracycline group of antibiotics.
4. A composition according to Claim 2 wherein the composition is formed into a shape of a strip average having a width of about 1mm, an average thickness of about 0.75mm, and an average length of about 10mm.
5. A composition according to Claim 2 wherein the composition is formed into the shape of a cone having an average length of about 15mm, an average diameter at the wide end of about 1.5mm, and an average diameter at the pointed end of about 0.25.

6. A composition according to Claim 2 wherein the composition is formed into the shape of a chip having an average length of about 15mm, an average width at the wide end of about 1.5mm, and an average width of the pointed end of about 0.5mm, and average thickness of about 0.8mm.
7. A composition according to Claim 6 wherein the polymer is ethylene vinyl acetate.
8. A composition according to Claim 7 wherein the active is selected from the tetracycline group of antibiotics.
9. A method of treating diseases of the oral cavity in a person or lower animal suffering from such disease by placing into the periodontal pocket or around said pocket or gingival sulcus of said person or lower animal a composition according to Claim 1.
10. A method according to Claim 9 wherein the drug active is selected from the tetracycline group of antibiotics.
11. A method according to Claim 10 wherein the composition is formed into the shape of a chip having an average length of about 10mm, an average width of the wide end of about 1mm, and an average width of the pointed end of about 0.2mm, and average thickness of about 0.6mm.
12. The use of the composition of any one of Claims 1-8 in a medicament for the treatment of diseases of the oral cavity.

## INTERNATIONAL SEARCH REP. T

International Application No

PCT/US 91/06397

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)<sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/22 A 61 K 9/70

## II. FIELDS SEARCHED

Minimum Documentation Searched<sup>7</sup>

Classification System

Classification Symbols

Int.Cl.5

A 61 K

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched<sup>8</sup>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>

Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
------------------------	--	-------------------------------------

X

EP,A,0140776 (THE FORSYTH DENTAL  
INFIRMARY FOR CHILDREN) 8 May 1985, see claims  
1-3; page 6, line 35 - page 7, line 18; page 7,  
line 30 - page 8, line 5; page 13, lines 2-15  
-----

1-4, 6-  
12<sup>10</sup> Special categories of cited documents:<sup>"A"</sup> document defining the general state of the art which is not considered to be of particular relevance<sup>"E"</sup> earlier document but published on or after the international filing date<sup>"T"</sup> document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<sup>"O"</sup> document referring to an oral disclosure, use, exhibition or other means<sup>"P"</sup> document published prior to the international filing date but later than the priority date claimed<sup>"T"</sup> later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<sup>"X"</sup> document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step<sup>"Y"</sup> document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.<sup>"A"</sup> document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

27-11-1991


Date of Mailing of this International Search Report

09.01.92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

 Danielle van der Haas

US 9106397  
SA 52082

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

**EPO FORM P0479**